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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	09/935,998	SIMONS, MALCOLM J.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2003 & 30 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-9,11-15,17-21,23 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-9,11-15,17-21,23 and 25-30* is/are rejected.

7)☒ Claim(s) *26-28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/2/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The specification remains objected to, as documents have been improperly incorporated by reference. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

Response to argument

2. At page 15 of the response received 03 October 2003 applicant asserts that there is no issue here as the specification is the same as that of the parent.

3. The above argument has been fully considered but is not found persuasive towards the withdrawal of the objection to the specification, as it does not point to where the cited documents are in fact properly incorporated by reference.

Claim Objections

4. A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim.

5. A claim, which depends from a dependent claim, should not be separated by any claim, which does not also depend from said dependent claim. In the present case, claims 26 and 267, which depend from claim 1, are separated from claim 1 by independent claims 13 and 19. Also, claim 28, which depends from claim 13, is separated from claim 13 by independent claim 19. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

6. Claim 12 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. For convenience, claim 12 is reproduced below.

> Claim 12. (original) The method of claim 1, wherein the amplified genomic DNA further comprises at least part of at least one exon.

Claim 1 requires the amplification of a "HLA genetic coding locus." By definition, the locus is genetic and it is coding. Further, coding regions are, by definition, exons. Therefore, claim 12 is not further limiting of claim 1.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 5-9, 11-15, 17-21, 23, and 25-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision of *Vas-Cath Inc. v. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

> This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 USC 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

9. For convenience, claims 1, 13, and 29, the only independent claims, are reproduced below.

Claim 1. (currently amended) A method of determining at least one haplotype encompassing a human HLA genetic coding locus comprising:

(a) amplifying human genomic DNA, wherein the amplified genomic DNA comprises a non-coding region sequence that is in genetic linkage with an ~~the~~ HLA genetic coding locus;

(b) detecting one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA genetic coding locus.

Claim 13. (currently amended) A method for determining at least one haplotype encompassing a multi-allelic human HLA genetic coding locus comprising:

(a) amplifying human genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said HLA genetic coding locus and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said at least one haplotype;

(b) analyzing the amplified DNA sequence to detect one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the multiallelic human HLA genetic coding locus.

Claim 19. (currently amended) A method for determining at least one haplotype encompassing a human HLA coding locus comprising:

(a) amplifying human genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said HLA coding locus;

(b) analyzing the amplified DNA sequence to detect one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA coding locus.

10. For purposes of examination, the phrase "genetic linkage" has been interpreted as encompassing the entire chromosome upon which the HLA complex is found (chromosome 6). Accordingly, claims 1, 13, and 19 have been interpreted as encompassing the amplification of entire chromosome 6.

11. The claims have been interpreted as encompassing the amplification of all of the loci, known and unknown, in a simultaneous manner, and wherein the amplicons for each of the loci

is of like size and is similarly labeled as with any other amplicon for different loci. It is noted that page 2, lines 24-25, of the disclosure teaches that the HLA complex comprises "at least 50 loci." Accordingly, the claimed method is considered to fairly encompass the simultaneous amplification and analysis of at least 50 different loci. Support for this interpretation is found in claims 3, 15, and 21, which recite, "two or more haplotypes are determined."

12. Claims 1, 13, and 19 are all limited in that the artisan is to identify "one or more sequence variations" of non-coding regions. The claims have been interpreted as encompassing the detection of any and all mutations of any and all possible HLA loci, be it in a simultaneous manner or otherwise. Said claims are also considered to encompass the identification of sequence variations in coding regions as well. With sequence variations for coding regions being missense, nonsense and silent, and represented through insertions, deletions, inversions, substitutions, and translocations.

13. As presently worded the claimed methods have also been interpreted as encompassing the use of any length and combination of primer as well as the generation of any size amplicon.

14. A review of the specification fails to find an adequate description of the claimed methods wherein primers of any length are to be used or where amplicons of any length are to be generated. Page 15 of the disclosure teaches that the amplicons are to range in size from 800 to 2000 nucleotides. It is further noted that at page 16, line 31, the amplicon can be 200 nucleotides in length, and at pages 89-90, Example 6 (prophetic) is presented wherein an amplicon of 72 bases could be produced. The specification does not teach the generation of larger or smaller sized nucleic acid fragments, nor the interpretation of nucleic acid fragments of different sizes. Attention is also directed to page 22 of the disclosure wherein is taught that the primers used in

the claimed methods are to range in size from 8 to 30 nucleotides. Accordingly, the specification does not reasonably support the position that applicant contemplated, much less possessed, methods where primers of lengths outside of 8 to 30 nucleotides were to be used or where amplicons other than from 72 to 2,000 nucleotides in lengths are produced and evaluated.

As presented above, the claimed method has been interpreted as encompassing the determination of any number of haplotypes in any number of human HLA loci, and that the method can be used to identify whether he individual, or its offspring, is susceptible to any disease. While the specification does provide a description of analyzing the HLA DQA1 locus in humans, the specification has not been found to provide the requisite description of such a broad genus as claimed. It would appear that applicant is attempting to assert that presently claimed genus is obvious in view of the disclosure. Obviousness, however, cannot be relied upon in satisfying the written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

15. A review of the specification finds the following examples:

- Example 1, "Forensic Testing," pages 78-80;
- Example 2, "Paternity Testing," pages 80-82;
- Example 3, "Analysis of HLA DQA1 Locus," pages 83-88;
- Example 4, "Analysis of HLA DQA1 Locus," page 88;
- Example 5, "DQA1 Allele-Specific Amplification," page 89;

- Example 6, "Detection of Cystic Fibrosis," pages 89-90;
- Example 7, "Analysis of Bovine Leukocyte Antigen Class I," pages 90-91; and
- Example 8, "Preparation of Primers," pages 91-93.

16. Pages 57-63 of the specification provide a listing of HLA loci-specific primers. Review of this listing finds that these primers are specific for the following loci: A, B, C, Class I, DQAI, DRA, DRB, DQB1, and DPB1. As noted above, the record clearly shows that the HLA complex comprises "at least 50 loci." In contrast, the specification provides primers for amplification of less than 20% of the loci. Such a showing does not provide an adequate written description of the primers that are required to conduct the required amplification, which as noted above, fairly encompasses the simultaneous amplification of all possible loci.

17. While amplification will result in the production of amplicons, the mere production of amplicons will not result in the determination of variations in a nucleotide sequence. Page 40, lines 18-31, teaches conducting sequencing reactions. The specification is essentially silent as to which mutations for any and al HLA loci are to be correlated, directly and indirectly, with any disease (claims 5 and 17). Assuming *arguendo*, that some mutations can be correlated with a disease, the specification is silent as to how one is to identify useful mutations from useless mutations when the disease is multigenic in origin and the genes, much less the mutation involved in causing the disease, are not known.

18. In accordance with claims 9 and 23, one is to analyze DNA from a crime-scene sample. Example 1, pages 78-80, is the only example that is relevant to these claims. As seen therein, one conducts a restriction endonuclease digestion of DNA extracted from blood cells, the restricted DNA is then subjected to amplification using locus-specific primers, and then but two

loci are amplified. Post amplification, the sizes of the amplicons is then compared. No effort is made to detect sequence variations, be they mutations associated with a disease, is non-coding regions. No effort is made to identify mutations found only on a coding region. While the claimed method fairly encompasses multiplex analysis, i.e., all of the amplification reactions take place in a common tube; Example 1 clearly shows that each amplification reaction was conducted in a separate tube. In contrast, the claimed method clearly requires one to identify any number of sequence variations where no endonuclease digestion occurs, and that all of the amplification reactions can take place in a multiplex format.

19. In view of the breadth of the claims' scope, and the limited guidance provided, the specification has not been found to provide an adequate written description of the claimed invention and in like manner, the specification does not reasonably suggest that applicant was in possession of the full scope of the now-claimed invention.

20. Claims 1-3, 5-9, 11-15, 17-21, 23, and 25-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see

> *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

21. As presented above, the specification has not presented an adequate written description of the claimed method. To the extent that the claims encompass embodiments not adequately described and a such, not reasonably suggested by the disclosure as being in applicant's possession at the time of filing, claims 1-3, 5-9, 11-15, 17-21, 23, and 25-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement as one cannot enable that which they do not have possession of.

22. The claimed method encompasses performing any number of amplification steps and where any level of stringency is used. To perform any number of amplification steps speak to the introduction of amplification artifacts due to error on the part of he polymerase as well as because of mis-priming, including primer-dimer formation. As a foundation, proper primer

hybridization requires specific hybridization conditions. As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

1. The purity of the nucleic acid preparation.

2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.

3. Length of homologous base sequences- any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.

4. Ionic strength- the rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- the presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- the longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- the presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

23. Additionally, the invention clearly relates to the analysis of human HLA alleles. The analysis of such alleles present additional difficulties. In support of this position, attention is directed to Canck et al. (US 2002/0197613 A1):

> The HLA system is the most polymorphic human genetic system yet known. HLA class I genes share a similar structure (from 5' to 3'): a S' untranslated flanking region, a first exon (exon 1) having a length of approximately 73 base pairs, a first intron (intron 1) having a length of approximately 130 base pairs, a second exon (exon 2), having a length of approximately 250 base pairs, a second intron (intron 2), having a length of approximately 272 base pairs, a third exon (exon 3), having a length of approximately 276 base pairs, a third intron (intron 3), having a length of approximately 588 base pairs and a fourth exon (exon 4), having a length of approximately 276 base pairs. Polymorphic substitutions within HLA class I alleles are mostly located in both exon 2 and exon 3, encoding the peptide binding groove of the class I molecule. . . Locus-specific primers are available for the amplification of these 1 kb amplicons. However, such large amplicons are difficult to amplify and show secondary structure formation resulting in inefficient hybridization of some probes. In addition, due to the emergence of new HLA-Class I alleles, certain allele combinations cannot be distinguished anymore by the detection of polymorphism's only in exon 2 and exon 3 and additional typing in exon 4 is required. This raises the need for the additional amplification of exon 4, resulting in an even larger amplicon. Therefore, a separate amplification of exon 2, exon 3 and/or exon 4 would be desired resulting in amplification products that enable a more efficient typing of HLA class I alleles. However, as locus-specific primer annealing sites are scarce and cannot be found in exon 2, exon 3 or exon 4, the separate and locus-

> specific amplification of exon 2, exon 3 and/or exon 4 of HLA-A, HLA-B or HLA-C is not that evident. (Emphasis added)

Attention is also directed to Baxter-Lowe et al.:

> The polymerase chain reaction (PCR) process, as described in Mullis U.S. Pat. No. 4,683,202, issued Jul. 28, 1987, allows the amplification of genomic DNA and has given rise to more convenient HLA typing procedures. HLA-DQ alpha and HLA-DP alpha and beta genes have been amplified, and then sequenced or hybridized with oligonucleotide probes. See Saiki et al., Nature, Vol. 324, pp. 163-166, 1986, Bugawan et al., J. Immunol., Vol. 141, No. 12, pp. 4024-4030, 1988, and Gyllensten et al., Proc. Natl. Acad. Sci. USA, Vol. 85, pp. 7652-7656, 1988. However, these methods have limited reliability due to the tendency of the probes to bind with greater or lesser specificity depending on the reaction conditions employed. (Emphasis added)

24. The specification is essentially silent as to how these art-recognized issues are to be overcome. Rather than setting forth an enabling disclosure, the public is being unfairly forced into enabling the claimed invention, assuming *arguendo*, that the claimed invention could be fully enabled. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1-3, 5-9, 11-15, 17-21, 23, and 25-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

25. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

26. Claims 1-3, 5-9, 11-15, 17-21, 23, and 25-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

27. Claims 1, 13, and 19 are indefinite in that the full name for the term recognized by the abbreviation "HLA" is not recited. Applicant is urged to consider using the full name, followed

by an abbreviation within parenthesis, at the first instance for each independent claim wherein the abbreviation is presently found. Claims 2-3, 5-9, 11, 12, 14, 15, 17-21, 23, and 25-30, which depend from said claims 1, 13, and 19, fail to overcome this issue and are similarly rejected.

28. Claims 1, 13, and 19 are indefinite with respect to just what constitutes the "HLA genetic coding locus." Page 2 of the specification teaches that there is a "HLA complex" that is in turn comprised of "at lest 50 loci." It is not clear, however, as to what constitutes a "HLA genetic coding locus." Acknowledgement is made of where at page 11, lines 3-9, that "an HLA locus is the region of the genomic DNA that includes the gene that encodes an HLA gene product." Such definition does not define "HLA genetic coding locus" for a locus, by definition, must already comprise a coding region, i.e., a gene. And given that a locus is to comprise a gene and is comprised of genetic material, it is unclear as to how a genetic coding locus is to be differentiated from a coding locus, or with simply a locus.

29. Claim 8 is indefinite in that it lacks antecedent support for "the coding region of the locus." Support does exist for "HLA genetic coding locus." Claim 8 is also indefinite with respect to its metes and bounds. In particular, does "the coding region of the locus" encompass coding regions (exons) of other genes that are in genetic linkage with the locus (e.g., found on he same chromosome, chromosome 6), or are they excluded? To the extent that translocational events take place, is the term to be construed so as to encompass exons from genes normally found on a different chromosome yet through translocation are now found on part of chromosome 6?

Double Patenting

30. The nonstatutory double patenting rejection of claims 1-9, 11-21, 23, and 25-46 as being unpatentable over claims 1-7 of U.S. Patent No. 5,192,659 has been withdrawn in view of the filing of a terminal disclaimer.

Claim Rejections - 35 USC § 103

31. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

32. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

33. Claims 1-3, 5-9, 11-15, 17-21, 23, 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,582,788 (Erlich) in view of EP 0256630 (Woo et al.).

34. Erlich, abstract, teaches a method for performing HLA typing and that the disclosed method permits paternity determinations as well as diagnosis of diseases and susceptibility to diseases.

35. Erlich, column 2, bridging to column 7, disclose a method for isolating DNA from a sample, cleaving the DNA through restriction endonucleases and thereby produce polymorphic patterns. Hybridization of a probe to the cleaved sample DNA will yield detectable polymorphic patterns that are in turn specific for a given HLA locus.

36. Column 6 discloses that analysis can be conducted for one or multiple HLA loci.

37. Erlich does not teach performing an amplification reaction.

38. Woo et al., page 7, teaches performing an analysis of sample DNA where mutations in non-coding and coding regions are evaluated. In particular, the mutation associated with phenylketonuria (PKU; applicant's claim 7).

39. Woo et al., page 10, teach performing genetic analysis on parents and their offspring.

40. Woo et al., pages 24-27, teach combining polymerase chain reaction with the method of nucleic acid analysis as such allows for detection of point mutations with greater ease as well as analysis of minute quantities of DNA.

41. Woo et al., page 27, provides a listing of genetic diseases/predisposition thereto that can be detected through performance of an amplification reaction.

42. In view of the teachings of the prior art, it would have been obvious to one of ordinary skill in the art at the time that the invention was made to have modified the method of Erlich with the amplification and detection method of Woo et al., so as to allow for the analysis of greater number of human HLA loci and the facile determination of mutations associated with a disease, or with an individual as it relates to paternity testing.

43. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1-3, 5-9, 11-15, 17-21, 23, 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 4,582,788 (Erlich) in view of EP 0256630 (Woo et al.).

Conclusion

44. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

45. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

46. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

47. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

48. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
16 March 2004